

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY


(Chapter II of the Patent Cooperation Treaty)

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(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PA0356 PCT		FOR FURTHER ACTION		See Form PCT/PEA416
International application No. PCT/GB2004/003341		International filing date (day/month/year) 30.07.2004	Priority date (day/month/year) 30.07.2003	
International Patent Classification (IPC) or national classification and IPC G01N33/50, G01N33/533				
Applicant AMERSHAM BIOSCIENCES UK LIMITED et al.				
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 7 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input checked="" type="checkbox"/> sent to the applicant and to the International Bureau a total of 11 sheets, as follows:</p> <p><input checked="" type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in Item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (Indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>				
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the opinion</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input checked="" type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input checked="" type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input type="checkbox"/> Box No. VIII Certain observations on the international application</p>				
Date of submission of the demand 11.02.2005		Date of completion of this report 28.11.2005		
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized Officer Pinheiro Vieira, E Telephone No. +49 89 2399-7865		

**INTERNATIONAL PRELIMINARY REPORT
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International application No.
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Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:

- ☐ international search (under Rules 12.3 and 23.1(b))
- ☐ publication of the international application (under Rule 12.4)
- ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

Description, Pages

1-4, 6-11, 13-15, 17-28

as originally filed

5, 12, 16

received on 04.08.2005 with letter of 03.08.2005

Claims, Numbers

1-26

received on 04.08.2005 with letter of 03.08.2005

Drawings, Sheets

1/5-5/5

as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☒ The amendments have resulted in the cancellation of:

- ☐ the description, pages
- ☒ the claims, Nos. 27
- ☐ the drawings, sheets/figs
- ☐ the sequence listing (*specify*):
- ☐ any table(s) related to sequence listing (*specify*):

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/figs
- ☐ the sequence listing (*specify*):
- ☐ any table(s) related to sequence listing (*specify*):

* If item 4 applies, some or all of these sheets may be marked "superseded."

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:
- ☐ the entire international application,
 - ☒ claims Nos. 15-24
because:
 - ☒ the said international application, or the said claims Nos. 15-24 relate to the following subject matter which does not require an international preliminary examination (specify):
see separate sheet
 - ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
 - ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
 - ☐ no international search report has been established for the said claims Nos.
 - ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
 - ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
 - ☐ See separate sheet for further details

**INTERNATIONAL PRELIMINARY REPORT
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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	2,3,7-13
	No: Claims	1,4-6,14-26
Inventive step (IS)	Yes: Claims	13
	No: Claims	1-12,14-26
Industrial applicability (IA)	Yes: Claims	1-14,25,26
	No: Claims	15-24

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

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Re Item III.

Claims 16-25 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V.

V.1 Reference is made to the following documents:

- D1 : WO 03/020294 A (SCHMIDT, ALFRED; WIELAND, HEINRICH) 13 March 2003 (2003-03-13)
- D2 : STRESSER D M ET AL: "A HIGH-THROUGHPUT SCREEN TO IDENTIFY INHIBITORS OF AROMATASE (CYP19)" ANALYTICAL BIOCHEMISTRY, ACADEMIC PRESS, SAN DIEGO, CA, US, vol. 284, no. 2, 2000, pages 427-430, XP000979096 ISSN: 0003-2697
- D3: WO 02/099424 A (AMERSHAM BIOSCIENCES UK LIMITED; SMITH, JOHN, ANTHONY; WEST, RICHARD,) 12 December 2002 (2002-12-12)

D1 discloses compounds having at least one detectable group where the compounds comprise an aromatase substrate. It further relates to diagnostic and therapeutic methods using said compounds.

D2 concerns a fluorometric substrate for aromatase (O-benzylfluorescein benzyl ester) and its use in a screening method.

D3 discloses acridone derivatives and their use as fluorescent labels in methods of screening and methods for labelling substrates.

V.2 Novelty, inventive step and industrial applicability (Art. 33 PCT).

- 2.1 The present application concerns compounds containing a fluorescent dye molecule (R) coupled to a substrate for aromatase (S) via a linker (L) with the formula R-L-S characterized in that the fluorescence signal of the compounds changes in respect of fluorescence lifetime when the compound is acted upon by an enzyme with

aromatase activity; use of compound for measuring aromatase activity in sample; diagnostic and screening methods.

- 2.2 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1, 4-6 and 14-26 is not new in the sense of Article 33(2) PCT in view of D2. Document D2 disclose changes of the fluorescent signal in respect of fluorescence lifetime when the compound is acted upon by an enzyme with aromatase activity.
- 2.3 It is at present not apparent to which problem the compounds of **formula (I)** where **R** is an acridone dye or quinacridone (claims 2 and 3), where **L** is the linker as defined in claims 7 or 8, and where **S** is the substrate as given in claims 9-12, could be a solution. Acridone dye derivatives are known from D3 as suitable fluorescence labels for labelling and lifetime detection of a target material, the substrates defined by claims 9-12 are known from D2, and the linkers **L** as claimed in claims 7 or 8 are well known chemical linkers for the skilled man.
The subject matter of claims 2, 3 and 7-12 is therefore, not inventive.
- 2.4 The problem to be solved by claim 13 in view of the closest prior art document D1, can be seen as the provision of further labelled substrates for aromatase. The Applicant solves the problem by providing the compounds of **formula XX** where the label is an acridone dye molecule linked via a linker to testosterone.

The application differs from D1 in that the label is an acridone dye. All over D1 description's there are references to labelled aromatase substrates (also testosterone) detectable by spectroscopic methods, and imaging methods adapted to the detectable group. Nevertheless, this document is silent as to the use of acridone dyes conjugated to testosterone.

Although, document D3 discloses acridone florescent dyes and their use as fluorescent probes this document does not suggest acridone dyes bound to the particular substrate testosterone.

D2 concerns another substrate labelled with flourescein.

In view of the prior art documents D1-D3 it is not obvious to provide the compounds of **formula XX** where testosterone is labelled with an acridone dye. Therefore, claim

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(SEPARATE SHEET)**

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14 is inventive.

2.5 The subject matter of claims 1-14, 25 and 26 is industrial applicable.